Relapses of sarcoidosis: what are they and can we predict who will get them?

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Can one predict who will relapse from sarcoidosis? <http://ow.ly/qYAP2>

Granulomatous inflammation in the lung may occur from a variety of causes. Many of these are the result of specific antigens that reach the lung and induce a granulomatous response. A prototype of this schema is pulmonary tuberculosis where the organism serves as the inciting antigen. Treatment of tuberculosis is aimed at killing and clearing the organism. It would be foolhardy and potentially lethal to solely treat the granulomatous inflammation of tuberculosis with immunosuppressive anti-granulomatous medications.

Sarcoidosis is, obviously, very different. The cause of sarcoidosis is unknown and treatment directed against the granulomatous inflammation is effective [1]. When anti-sarcoidosis medications are withdrawn, relapse is very common. Reported relapse rates of sarcoidosis range from 13% to 75% depending on the population studied [2–5]. These relapses typically occur 1 month to 1 year after therapy is tapered or discontinued [4, 5].

In most studies, the definition of relapse has been vague. In some cases, recurrence of the disease may be considered an acute exacerbation of the sarcoidosis [6]. In other situations, the disease may have never really been under control, but simply the manifestation became more apparent as anti-inflammatory drugs were withdrawn. In addition, progression of sarcoidosis is not well defined. We propose a series of criteria to define progression of the disease (table 1). These include a significant need to increase systemic anti-inflammatory medications, for example increasing the dose of glucocorticoids or the addition of other agents such as infliximab. This would not include the addition of a new agent simply for steroid sparing. In sarcoidosis patients with disease for the past 5 years, about 10% will have had an increase in their anti-inflammatory medicines in the previous year [7]. A worsening of chest imaging has been seen in many, but not all, patients with clinical worsening. A worsening of imaging correlated with worsening pulmonary function [8–10]. A clinically significant change in pulmonary function has been reported with several treatments for worsening sarcoidosis [11]. Changes in forced vital capacity and diffusing capacity of the lung for carbon monoxide are associated with increased mortality in idiopathic pulmonary fibrosis [12]. A major predictor of need for chronic therapy has been dyspnoea [13]. We feel that the presence of one or more of these features would be considered progression of the disease.

Interestingly, one of the risk factors associated with a high rate of sarcoidosis relapse is the previous use of corticosteroids [4, 14]. In addition, a risk factor for continued use of corticosteroid therapy 2 years after the diagnosis of sarcoidosis is use of corticosteroids at the initial visit [13]. Recent genetic studies have indicated that the presence of certain human leukocyte antigens or other factors is associated with a high rate of spontaneous resolution [15] or chronic disease [16–18].

The data above suggest that these exacerbations of sarcoidosis may possibly not truly be relapses, but rather situations where the disease never really “left” and the granulomatous response to whatever causes sarcoidosis was only temporarily compromised while immunosuppressive therapy was being used. Since we

Received: Aug 09 2013 | Accepted after revision: Nov 05 2013

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TABLE 1 Definition of progression of sarcoidosis

Significant increase in systemic medication
Worsening of chest imaging
Worsening of pulmonary function status
Worsening of dyspnoea

do not know if sarcoidosis is caused by antigens, much less any specific ones, it is not presently possible to determine when the “cause” of sarcoidosis has been cleared and the disease is truly in remission. Unfortunately, all of our previously available markers for active granulomatous inflammation in sarcoidosis, including serum angiotensin-converting enzyme [19], gallium-67 scan results [20] and bronchoalveolar lavage analysis [21], are often suppressed on effective therapy and are not predictive of relapse. In particular gallium-67 uptake is rapidly suppressed by glucocorticoids independent of the effect of glucocorticoids on the sarcoidosis itself [20].

Infliximab has proved an effective form of therapy for refractory pulmonary and extrapulmonary disease [22–24]. However, infliximab treatment often has to be stopped due to allergic reactions, infections or cost issues [25, 26]. Sarcoidosis patients treated with infliximab appear to have a very high likelihood of relapse of their disease when the drug is discontinued [27, 28]. In one study in which the drug was withdrawn after 1 year or less, 90% of patients had recurrence of their symptomatic disease [28]. This high rate of relapse is similar to what has been recorded in rheumatoid arthritis patients [29].

It is against this backdrop that VORSELAARS *et al.* [30] report their retrospective analysis concerning the outcome of 47 sarcoidosis patients who discontinued infliximab therapy. The study proposed to stop the drug after 6 months in all patients. 62% of patients experienced a relapse of disease after drug withdrawal. With this large and well-defined population, the authors were able to examine several potential markers for predicting relapse. The soluble interleukin (IL)-2 receptor and ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography (PET) scan at the end of infliximab treatment were independent predictors of relapse.

The soluble IL-2 receptor reflects the activation of CD4 T-lymphocytes and others have reported it as a marker of disease activity [31, 32]. In comparison to other serum markers, it appears to be as predictive of disease activity [33, 34]. It has also been found to be complimentary to FDG PET scanning by other authors [35]. However, the marker has some variability and is not specific for lung disease [33].

The FDG PET scan has the advantage of detecting organ specific inflammation [36]. Previous reports have indicated that presence of parenchymal lung activity is associated with clinical deterioration over the next 6 months [37, 38]. Unlike the gallium scan, which is suppressed by glucocorticoids, FDG PET scans can remain markedly positive in sarcoidosis patients who are failing treatment [39]. Thus, FDG PET appears useful in assessing the response to treatment in refractory sarcoidosis.

The study by VORSELAARS *et al.* [30] demonstrates the utility of soluble IL-2 receptor and FDG PET scanning in managing sarcoidosis patients. Further studies will be needed to confirm this observation, but these findings may have major clinical and financial impact. While the FDG PET scan is an expensive test, the judicious use of FDG PET may allow the clinician to discontinue an even more expensive, as well as potentially more dangerous, treatment regimen. Furthermore, persistence of soluble IL-2 receptor elevation and positive FDG PET scan findings support the notion that many sarcoidosis relapses actually represent chronic disease that was suppressed by immunosuppression and remission was really never achieved.

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